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E "TACE"/CN 25

L1 2 S E3

FILE 'MEDLINE, AGRICOLA, CAPLUS, BIOSIS, EMBASE, WPIDS' ENTERED AT
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L2 4599 S L1 OR TACE OR ADAM-17 OR ADAM17 OR (TUMOR (W) NECROSIS (W) FA

L3 81 S L2 AND CRYSTAL

L4 45 DUP REM L3 (36 DUPLICATES REMOVED)

L5 3 S L4 AND ((SPACE (W) GROUP) OR (UNIT (W) CELL))

FILE 'CAPLUS' ENTERED AT 10:30:21 ON 26 JUN 2006

E BLACK R A/AU 25

L6 40 S (E3 OR E114 OR E115 OR E116) AND (L1 OR TACE OR ADAM-17 OR AD
E PAXTON R J/AU 25

L7 8 S (E3 OR E9 OR E10 OR E11) AND (L1 OR TACE OR ADAM-17 OR ADAM17
E BODE W/AU 25

L8 2 S (E3 OR E4 OR E5 OR E17) AND (L1 OR TACE OR ADAM-17 OR ADAM17
E BODE W/AU 25

E MASKOS K/AU 25

L9 6 S (E3 OR E5) AND (L1 OR TACE OR ADAM-17 OR ADAM17 OR (TUMOR (W)
E FERNANDEZ CATALAN C/AU 25

L10 2 S (E3 OR E4) AND (L1 OR TACE OR ADAM-17 OR ADAM17 OR (TUMOR (W)
E CHEN J MING/AU 25

E CHEN JAMES MING/AU 25

L11 11 S (E3) AND (L1 OR TACE OR ADAM-17 OR ADAM17 OR (TUMOR (W) NECRO
E LEVIN J I/AU 25

L12 58 S (E3 OR E51 OR E52 OR E53 OR E54) AND (L1 OR TACE OR ADAM-17 O

L13 6 S (L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12) AND CRYSTAL

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☒ 2A8H



Characteristics
Classification
Compound
Authors

Crystal structure of catalytic domain of TACE with Thiomorpholine Sulfonamide Hydroxamate inhibitor

Release Date: 07-Feb-2006 Exp. Method: X Ray Diffraction

Resolution: 2.30 Å
Hydrolase

Mol. Id: 1 Molecule: Adam 17 Fragment: Catalytic Domain Mutation: S266A, N452Q
Levin, J.I., Chen, J.M., Laakso, L.M., Du, M., Schmid, J., Xu, W., Cummons, T., Xu, J., Jin, G., Barone, D., Skotnicki, J.S.

☒ 1ZXC



Characteristics
Classification
Compound
Authors

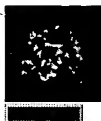
Crystal structure of catalytic domain of TNF-alpha converting enzyme (TACE) with inhibitor

Release Date: 27-Sep-2005 Exp. Method: X Ray Diffraction

Resolution: 2.28 Å
Hydrolase

Mol. Id: 1 Molecule: Adam 17 Mutation: YES
Levin, J.I., Chen, J.M., Laakso, L.M., Du, M., Du, X., Venkatesan, A.M., Sandanayaka, V., Zask, A., Xu, J., Xu, W., Zhang, Y., Skotnicki, J.S.

☒ 2DDF



Characteristics
Classification
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Authors

Crystal structure of TACE in complex with TAPI-2

Release Date: 14-Mar-2006 Exp. Method: X Ray Diffraction

Resolution: 1.70 Å
Hydrolase

Mol. Id: 1 Molecule: Adam 17 Mutation: S266A, V353G, Q452N
Ingram, R.N., Orth, P., Strickland, C.L., Le, H.V., Madison, V., Beyer, B.M.

☒ 2FV9



Characteristics
Classification
Compound
Authors

Crystal structure of TACE in complex with JMV 390-1

Release Date: 14-Mar-2006 Exp. Method: X Ray Diffraction

Resolution: 2.02 Å
Hydrolase

Mol. Id: 1 Molecule: Adam 17 Mutation: S266A, V353G, Q452N
Ingram, R.N., Orth, P., Strickland, C.L., Le, H.V., Madison, V., Beyer, B.M.

☒ 1BKC



Characteristics
Classification
Compound
Authors

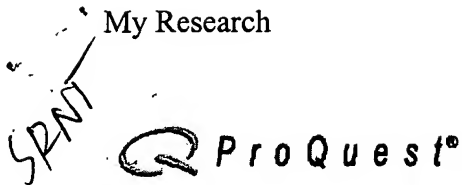
CATALYTIC DOMAIN OF TNF-ALPHA CONVERTING ENZYME (TACE)

Release Date: 22-Jun-1999 Exp. Method: X Ray Diffraction

Resolution: 2.00 Å
Zn Endopeptidase

Mol. Id: 1 Molecule: Tumor Necrosis Factor Alpha Converting Enzyme Mutation: S266A, N452Q Mol. Id: 2 Molecule: Tumor Necrosis Factor Alpha Converting Enzyme Mutation: S266A, N452Q Mol. Id: 3 Molecule: Tumor Necrosis Factor Alpha Converting Enzyme Mutation: S266A, N452Q Mol. Id: 4 Molecule: Tumor Necrosis Factor Alpha Converting Enzyme Mutation: S266A, N452Q
Maskos, K., Fernandez-Catalan, C., Huber, R., Bourenkov, G.P., Bartunik, H., Ellestad, G.A., Reddy, P., Wolfson, M.F., Rauch, C.T., Castner, B.J., Davis, R., Clarke, H.R., Petersen, M., Fitzner, J.N., Cerretti, D.P., March, C.J., Paxton, R.J., Black, R.A., Bode, W.

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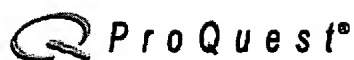
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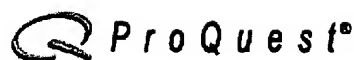
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- ☐ 2. **Ectodomain shedding of the epidermal growth factor receptor ligands: Mechanisms and regulation**
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- ☐ 3. **Functional characterization of the TNFalpha convertase (TACE) and its role in shedding**
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- ☐ 5. **Die proteolytische Freisetzung des membranständigen CD30 durch das Tumor-Nekrose [Alpha] konvertierende Enzym TACE (ADAM-17)**
by *Dietrich, Sebastian*, Dr., Christian-Albrechts Universität zu Kiel (Germany), 2003; AAT 3134727
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- ☐ 6. **The ADAMs: A novel family of cell surface proteins with adhesive and protease activity**
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- ☐ 13. **Rôle des convertases de proprotéines et des metalloprotéases dans la maturation de la metalloprotéase TACE**
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- ☐ 19. **Die Bestimmung verschiedener Laborparameter zur Erfolgskontrolle nach transarter Chemoemolisation (TACE) des hepatozellularen Karzinoms**
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- ☐ 20. **Biochemical and functional analysis of metalloprotease-disintegrins and ectodomain**
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☐ **1: tumor necrosis factor-alpha convertase [Substance Name]**

a membrane zinc-containing endopeptidase; SPRACT is an isoform of ADAM17 corresponding to the cytoplasmic domain; RefSeq NM_009615 (Adam17, mouse); NM_003183 (ADAM17, human); NM_020306 (rat)
Date introduced: October 4, 1996

Registry Number: EC 3.4.24.-

Heading Mapped to:

- [ADAM Proteins](#)

Entry Terms:

- ADAM-17
- TACA (enzyme)
- TNF-alpha converting enzyme
- a disintegrin and metalloprotease domain 17 protein
- ADAM17 protein
- tumor necrosis factor alpha convertase
- tumor necrosis factor-alpha converting enzyme
- TACE (enzyme)
- Adam17 protein, rat
- a disintegrin and metalloproteinase domain 17 protein, rat
- tumor necrosis factor, alpha, converting enzyme, rat
- TACE protein, rat
- ADAM17 protein, human
- a disintegrin and metalloproteinase domain 17 protein, human
- tumor necrosis factor, alpha, converting enzyme, human
- TACE protein, human
- Adam17 protein, mouse
- Tace protein, mouse
- a disintegrin and metalloproteinase domain 17 protein, mouse
- TNF-alpha converting enzyme, mouse
- SPRACT protein, human

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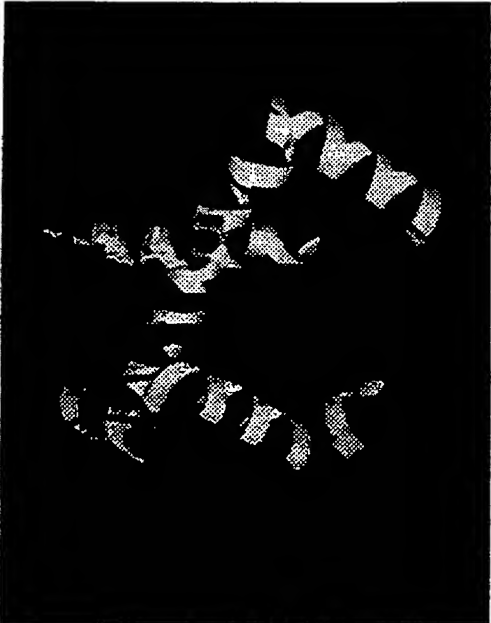
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			(43) International Publication Date: 12 August 1999 (12.08.99)
(21) International Application Number: PCT/US99/02185 (22) International Filing Date: 3 February 1999 (03.02.99) (30) Priority Data: 60/073,709 4 February 1998 (04.02.98) US 09/050,083 30 March 1998 (30.03.98) US Not furnished 27 January 1999 (27.01.99) US (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Applications US 60/073,709 (CON) Filed on 4 February 1998 (04.02.98) US 09/050,083 (CON) Filed on 30 March 1998 (30.03.98) US Not furnished (CON) Filed on 27 January 1999 (27.01.99) (71) Applicants (for all designated States except US): IMMUNEX CORPORATION [US/US]; 51 University Street, Seattle, WA 98101 (US). MAX-PLANCK-INSTITUTE FOR BIO-CHEMISTRY [DE/DE]; Am Klopferitz 18a, D-82152 Martinsreid-Planegg (DE). AMERICAN HOME PRODUCTS CORPORATION [US/US]; 5 Giralda Farms, Madison, NJ 07940 (US).		(72) Inventors; and (75) Inventors/Applicants (for US only): BLACK, Roy, A. [US/US]; 8062 30th Avenue N.E., Seattle, WA 98115 (US). PAXTON, Raymond, James [US/US]; 6583 156th Avenue S.E., Bellevue, WA 98006 (US). BODE, Wolfram [DE/DE]; Tulpenstrasse 5, D-82131 Gauting (DE). MASKOS, Klaus [DE/DE]; Roggersdorferstrasse 36, D-83607 Holzkirchen (DE). FERNANDEZ-CATALAN, Carlos [ES/DE]; Am Klopferitz 18a, D-82152 Martinsreid-Planegg (DE). CHEN, James, Ming [US/US]; 7 Sargent David Stoddard Court, Bedminster, NJ 07921 (US). LEVIN, Jeremy, Ian [US/US]; 19 Long Meadow Drive, New City, NY 10956 (US). (74) Agents: ISACSON, John, P. et al.; Foley & Lardner, Suite 500, 3000 K Street, N.W., Washington, DC 20007-5109 (US). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments. (88) Date of publication of the international search report: 7 October 1999 (07.10.99)	
(54) Title: CRYSTALLINE TNF- α -CONVERTING ENZYME AND USES THEREOF			
(57) Abstract			
<p>A tumor necrosis factor-α converting enzyme (TACE) is produced, purified, and crystallized. The three-dimensional coordinates of the crystal are obtained by X-ray diffraction. The coordinates can be recorded on a computer readable medium, or are part of a video memory, where they can be used as part of a system for studying TACE. The coordinates are also used in designing, screening, and developing compounds that associate with TACE.</p>			

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BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
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CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/02185

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N9/64

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 41624 A (IMMUNEX CORP) 27 December 1996 (1996-12-27) cited in the application	1-6, 9-14, 23-49, 52-57
Y	page 7, paragraph 3 page 18, last paragraph - page 19, paragraph 1	7,8, 15-22, 50,51, 58-63
X	WO 97 35538 A (GLAXO GROUP LTD ;MCGEEHAN GERARD M (US); CHEN WEN JI (US); MOSS MA) 2 October 1997 (1997-10-02)	1-6, 9-14, 23-49, 52-57
Y	page 28, last paragraph - page 29, paragraph 1	7,8, 15-22, 50,51, 58-63

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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

11 August 1999

Date of mailing of the international search report

18. 08. 99

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Authorized officer

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/02185

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>CIRILLI ET AL: "2.ANG. X-ray structure of adamalysin II complexed with a peptide phosphonate inhibitor adopting a retro-binding mode"</p> <p>FEBS LETTERS, vol. 418, 1 January 1997 (1997-01-01), pages 319-322, XP002089575 ISSN: 0014-5793 the whole document</p>	<p>7,8, 15-22, 50,51, 58-63</p>
Y	<p>--- GOMIS-RÜTH F ET AL: "Structures of adamalysin II with peptide inhibitors. Implications for the design of tumor necrosis factor alpha convertase inhibitors"</p> <p>PROTEIN SCIENCE, vol. 7, February 1998 (1998-02), pages 283-292, XP002111816 page 288; figures 6,7</p>	<p>7,8, 15-22, 50,51, 58-63</p>
Y	<p>--- US 5 594 106 A (FITZNER JEFFREY N ET AL) 14 January 1997 (1997-01-14) cited in the application the whole document</p>	<p>7,8,50, 51</p>
Y	<p>--- DECICCO, CARL P. ET AL: "Novel cyclophane inhibitors of matrix metalloproteinases and TNF -alpha converting enzyme."</p> <p>ABSTRACTS OF PAPERS AMERICAN CHEMICAL SOCIETY, (1997) VOL. 214, NO. 1-2, PP. MEDI 96. MEETING INFO.: 214TH AMERICAN CHEMICAL SOCIETY NATIONAL MEETING LAS VEGAS, NEVADA, USA SEPTEMBER 7-11, 1997, XP002111817 abstract 096</p>	<p>7,8,50, 51</p>
Y	<p>--- US 5 702 935 A (SACCHETTINI JAMES ET AL) 30 December 1997 (1997-12-30) example A</p>	<p>17,19</p>
A	<p>--- WO 97 08300 A (ARIAD PHARMA INC) 6 March 1997 (1997-03-06) cited in the application page 1-39; claims; figure 8</p>	<p>23-40</p>
A	<p>--- WO 97 15588 A (AZZO ALESSANDRA D ;RUDENKO GABRIELLE (US); HOL WIM G J (US)) 1 May 1997 (1997-05-01) cited in the application page 1-19; claims; figure 22</p>	<p>23-40</p>

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/02185

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p>MASKOS K ET AL: "Crystal structure of the catalytic domain of human tumor necrosis factor-alpha-converting enzyme." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1998 MAR 31) 95 (7) 3408-12., XP002111818 the whole document -----</p>	1-63

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/02185

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 23-40 could be considered as a mere presentation of information or a computer program, Rule 39.1 (v and vi) PCT, the search has been carried out as far as possible in our systematic documentation
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/02185

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